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Plants come to mind: phytocannabinoids, endocannabinoids and the control of seizures

JORDAN S. FARRELL and **IVAN SOLTESZ**

Department of Neurosurgery, Stanford University, Stanford, CA, USA

IVAN SOLTESZ: isoltesz@stanford.edu

Abstract

A growing body of evidence highlights that the endogenous cannabinoid (endocannabinoid) system is a key target for seizure control. Plant-derived cannabinoids have several endocannabinoid and related mechanisms that may be fundamental to their anti-seizure properties.

Keywords

Cannabis; CB1; CBD; epilepsy; FAAH; marijuana; seizure; THC

Epilepsy is a common neurological disease that is refractory to treatment in a third of cases —a proportion that has seemingly not changed for more than a century, despite the development of new medications [1]. Clearly, there is an unmet need for fundamentally new anti-epileptic drug targets and mounting evidence suggests that the endogenous cannabinoid (i.e. endocannabinoid: eCB) system is a prime candidate. The brain's endocannabinoid system is centered around the cannabinoid type-1 (CB1) receptor, which was discovered to be the receptor for Δ9-tetrahydrocannabinol (THC) [2]—the cannabis compound to which marijuana's psychological effects are most often attributed. Importantly, the molecular components for endocannabinoid synthesis, transport, receptor signaling and degradation are dysregulated in epilepsy, and drugs that alter this system profoundly modify seizure expression [3]. Synthetic drugs that specifically target elements of the endocannabinoid system have not yet made it to market, but perhaps medical cannabis and cannabis extracts may be useful to target this system for seizure control. Here we examine potential mechanisms by which the plant-derived cannabinoids, THC and cannabidiol (CBD), interact with the endocannabinoid system to modify seizure manifestation and discuss important outstanding questions regarding their treatment of epilepsy.

The CB1 receptor is the most common G-protein coupled receptor in the brain and regulates many neural circuits that mediate important behaviors through control of acute neurotransmission, long-term synaptic strength and synaptic integration [4–6]. The ubiquity and importance of the eCB system make it a great potential mechanism for seizure control where the goal is to suppress excessive network excitability and synchrony. Indeed,

Declaration of interests

None.

cannabinoids achieve this goal throughout a wide range of animal models [3]. However, administration of CB1 agonists, such as THC, may not appropriately target the endocannabinoid system to address the disrupted signaling in epilepsy, and is likely to have side effects. The timing of synthesis, release, receptor activation and degradation of the two major eCBs, 2-arachidonoyl glycerol ester (2-AG) and anandamide (AEA), are tightly regulated in a cell-type-specific manner and localized to discrete subcellular domains [7,8]. Systemically administered THC binds to available receptors without precise spatial or temporal specificity. It is not surprising, therefore, that THC is capable of side effects which include acute cognitive impairment and potential developmental abnormalities. Furthermore, CB1 agonists can paradoxically enhance network synchrony in some circuits by suppressing inhibitory neurotransmission [9] and potentially be seizure-promoting. Thus, THC and other CB1 agonists have some drawbacks, and may not invariably ameliorate seizures.

Unlike THC, CBD, which has gained momentous traction as an epilepsy therapeutic following two recent clinical trials for rare and highly refractory developmental epilepsies [10,11], is generally thought to exert its actions independent of the CB1 receptor. However, recent evidence supports that CBD opposes the actions of exogenous and endogenous cannabinoid agonists, including THC, through negative allosteric modulation [12]. CBD has been reported to act on more than 65 potential molecular targets [13]. Notably, the CBD dosage used in recent pediatric epilepsy trials, 20 mg/kg/day, is up to 100 times higher than dosages marketed to treat anxiety in adults, which generally recommend capsules that contain a total of 10–35 mg. Thus, at the high doses used to treat epilepsy, many mechanisms are probably at play, including endocannabinoid and related signaling pathways, discussed below.

One potential anti-seizure mechanism of CBD is through inhibition of an enzyme that metabolizes AEA—fatty acid amide hydrolase (FAAH) [14]. Unlike broad CB1 agonism, which is not synapse-specific, FAAH inhibition augments levels of AEA, whose synthesis and release is tightly controlled both temporally and spatially at specific synapses. FAAH inhibition was directly compared to broad CB1 agonism in a recent study using acute electrically evoked seizures in rats [15]. Both drugs inhibited seizures in a CB1-dependent manner; however, only FAAH inhibition restored the induction of long-term potentiation (LTP), a relevant synaptic memory mechanism which becomes impaired following repeated seizures. As both strategies act on the same receptor but have different effects on memory processes, these results emphasize the importance of spatiotemporally controlled eCB signaling. Regarding CBD, it is difficult to understand to what extent the anti-seizure effects act through FAAH inhibition, as CBD’s actions as a negative allosteric modulator of CB1 could mask a CB1-dependent effect while still permitting non-CB1-dependent effects.

Recent evidence indicates that CBD can control seizures via the activity of non-canonical cannabinoid receptors. In an animal model of Dravet syndrome (SCN1a+/− mice), GPR55, an orphan G-protein coupled receptor which is activated by eCBs, was necessary for the anti-epileptic properties of CBD [16]. Recent evidence also supports a role for transient receptor potential vanilloid 1 (TRPV1), which is activated by AEA, in CBD’s anti-seizure properties with corneal-kindling [17]. CBD, AEA and other vanilloid agonists are capable of activating and rapidly desensitizing TRPV1 channels [18], which potentially underlies this

anti-seizure effect of CBD. Interestingly, TRPV1 recruitment by FAAH inhibition results in a decrease in tonic 2-AG signaling at the CB1 receptor [19], resulting in altered endocannabinoid tone. The inherent cross-talk within and between lipid signaling systems, including endocannabinoid, endovanilloid, prostanoid and others, makes it likely that CBD affects many signaling domains, even if only a few key mechanisms are involved. Given the key role for disrupted eCB signaling in several epilepsies, a more complete understanding of CBD's control of eCB signaling could potentially be harnessed to identify which epilepsies would most benefit from CBD.

Despite the excitement surrounding CBD use in epilepsy, several important questions remain open. It is important to identify if CBD displays anti-seizure effects in more common drug-resistant epilepsies, such as temporal lobe epilepsy. Testing CBD in models of chronic, acquired epilepsy that display the hallmark of dysregulated endocannabinoid signaling is critical for this understanding. It is also unclear if CBD could be harmful to development, as a drug with broad mechanisms of action could influence many developmental trajectories. Regarding THC, an interesting outstanding question is whether CB1 agonism has anti-seizure effects by gating neurotransmitter release [4] or through post-synaptic control of synaptic integration [6]. To facilitate answers to these questions and take advantage of modern neuroscience tools, fewer restrictions for access to phytocannabinoids is necessary.

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References

1. Löscher W, Schmidt D Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia 2011; 52: 657–78. [PubMed: 21426333]
2. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990; 346: 561–4. [PubMed: 2165569]
3. Soltesz I, Alger BE, Kano M, Lee SH, Lovinger DM, Ohno-Shosaku T et al. Weeding out bad waves: towards selective cannabinoid circuit control in epilepsy. Nat Rev Neurosci 2015; 16: 264–77. [PubMed: 25891509]
4. Wilson RI, Nicoll RA Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 2001; 410: 588–92. [PubMed: 11279497]
5. Chávez AE, Chiu CQ, Castillo PE TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. Nat Neurosci 2010; 13: 1511–8. [PubMed: 21076423]
6. Maroso M, Szabo GG, Kim HK, Alexander A, Bui AD, Lee SH et al. Cannabinoid control of learning and memory through HCN channels. Neuron 2016; 89: 1059–73. [PubMed: 26898775]
7. Lee SH, Földy C, Soltesz I Distinct endocannabinoid control of GABA release at perisomatic and dendritic synapses in the hippocampus. J Neurosci 2010; 30: 7993–8000. [PubMed: 20534847]
8. Dudok B, Barna L, Ledri M, Szabó SI, Szabadits E, Pintér B et al. Cell-specific STORM super-resolution imaging reveals nanoscale organization of cannabinoid signaling. Nat Neurosci 2015; 18: 75–86. [PubMed: 25485758]
9. Sales-Carbonell C, Rueda-Orozco PE, Soria-Gómez E, Buzsáki G, Marsicano G, Robbe D Striatal GABAergic and cortical glutamatergic neurons mediate contrasting effects of cannabinoids on cortical network synchrony. Proc Natl Acad Sci USA 2013; 110: 719–24. [PubMed: 23269835]

10. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017; 376: 2011–20. [PubMed: 28538134]
11. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M et al. Effect of Cannabidiol on drop seizures in the Lennox–Gastaut syndrome. N Engl J Med 2018; 378: 1888–97. [PubMed: 29768152]
12. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol 2015; 172: 4790–805. [PubMed: 26218440]
13. Bih CI, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ Molecular targets of cannabidiol in neurological disorders. Neurotherapeutics 2015; 12: 699–730. [PubMed: 26264914]
14. Bisogno T, Hanuš L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001; 134: 845–52. [PubMed: 11606325]
15. Colangeli R, Pierucci M, Benigno A, Campiani G, Butini S, di Giovanni G The FAAH inhibitor URB597 suppresses hippocampal maximal dentate afterdischarges and restores seizure-induced impairment of short and long-term synaptic plasticity. Sci Rep 2017; 7: 11152. [PubMed: 28894217]
16. Kaplan JS, Stella N, Catterall WA, Westenbroek RE Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proc Natl Acad Sci USA 2017; 114: 11229–34. [PubMed: 28973916]
17. Whalley BJ, Gray RA, Stott CG, Jones NA Antiseizure properties of cannabidiol (CBD) are attenuated in the absence of transient receptor potential vanilloid 1 (TRPV1) receptors (S53.004). Neurology 2018; 90.
18. Iannotti FA, Hill CL, Leo A, Alhusaini A, Soubrane C, Mazzarella E et al. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels *in vitro*: potential for the treatment of neuronal hyperexcitability. ACS Chem Nerosci 2014; 5: 1131–41.
19. Lee SH, Ledri M, Tóth B, Marchionni I, Henstridge CM, Dudok B et al. Multiple forms of endocannabinoid and endovanilloid signaling regulate the tonic control of GABA release. J Neurosci 2015; 35: 10039–57. [PubMed: 26157003]